I wish to express my thanks to the Honorary Surgeons at the Birmingham and Midland Eye Hospital for their kindness in giving me permission to use the various notes and case sheets on the above cases, and also to Miss Marshall, Assistant Pathologist, who has done so much of the bacteriological investigation.

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ANNOTATIONS

RECENT PROGRESS IN ARSENICAL COMPOUNDS

The present day galaxy of drugs of the sulphonamide and allied groups, of which a new member appears on the therapeutic horizon every few months, appears to reflect a comparative lack of progress in the development of new organic arsenical compounds. We are apt to forget that in the decade following the introduction of the original salvarsan (606) and neo-salvarsan (914) many other organic arsenical preparations were launched for experimental and clinical work in syphilis. Many of their names are now scarcely known to the younger generation of workers in this therapeutic field. They represented the outcome of intense activity on the part of research chemists and manufacturers as well as steady patient trials on the part of the clinicians. Some of these compounds were used extensively in this country. Silver-salvarsan and neo-silver-salvarsan, with their additional component of silver, were used for many years with good results. Galyl, tetraoxy diphosphotetra-amino-diarsenobenzene, which was unique in including phosphorus in its structure was in use from 1913 until the early 1920's. Sulphoxyl-salvarsan, although apparently not a true salvarsan derivative, achieved a modest popularity particularly for resistant syphilis also in the 1920's.

Many other arsenical compounds appeared in these active years which saw the birth of sulpharsphenamine, stabilarsan, tryparsamide, stovarsol and acetylarsan, all of which have stayed in use until today. Others such as luargol, an antimony arsenobenzol preparation, ludyl, Albert 202, hectine, arsenomyl and arsaminol have fallen out of use long ago. Their names are now but a dim memory.

Little further progress was made until a re-investigation of the properties of *m*-amino-*p*. hydroxyphenylarsine oxide by Tatum and Cooper. This substance frequently termed "arsenoxide" had been suggested by Ehrlich as the active principle emanating from the breakdown of salvarsan but its toxicity for the lower animals appeared then too great to consider its use in human therapeutics. Tatum and Cooper in 1934 considered that "arsenoxide" possessed a therapeutic index in syphilis equal to or greater than most other effective agents, also that in rabbit syphilis this index was higher than for any other single antisyphilitic agent known to them. This compound now in use under the name of "Mapharsen," has made great headway in therapeutics since 1935 particularly in the United States of America where it has been used extensively for the treatment of syphilis along customary lines as well as for intensive arsenotherapy. In this country, where it is known as Mapharside, its employment is on a smaller scale. A recent report by Ross (1943) in 150 cases indicates satisfactory results.

Trisodarsen

Progress along these lines has continued. Stokes and Beerman in 1937 gave an account of a five year period study of the value in syphilis of a new member of the sulpharsphenamine series, tri-sodium-sulpharsphenamine, known as

Trisodarsen. This compound, which was prepared by Raiziss is the tri-sodium salt of 3·3¹ diamino 4·4¹ dihydroxy arsenobenzene N.N¹ di-methylene sulphonic acid.

An extended report of this trial of Trisodarsen at the Hospital of the University of Pennsylvania in an additional 361 patients has recently appeared from the hands of Beerman, Pariser and Gordon (1942). These workers found that the time required for the disappearance of *S. pallida* from the surface lesions of early syphilitic infections was usually less than ninety-six hours. The healing rate of these early lesions and the rate of reversal of positive serological reactions appeared more speedy than that effected by Mapharsen although inferior to arsphenamine in rapidity. Signs of intolerance from Trisodarsen, although chiefly of mild degree, were frequently encountered (44 per cent) but, apart from nitritoid crises which rarely occurred (0·6 per cent) these ensued at about the same frequency as with other organic arsenicals. Of the total of 550 patients there were seven cases of exfoliative dermatitis, four of haemorrhagic purpura and two fatal cases of aplastic anaemia. As is usual with compounds of this nature some patients were able to tolerate Trisodarsen after exhibiting a mild reaction to one of the other arsenical compounds. Conversely, some fifteen patients out of twenty-four who were intolerant to Trisodarsen continued treatment uneventfully with another trivalent arsenical.

In patients with early syphilis the positive blood reaction was reversed in seventy-five per cent after treatment over an average period of thirty-five days for primary cases and eighty-eight days for secondary cases. Some but not all these cases received additional bismuth therapy and in this connexion it was noted, as had previously been noted by Beerman (1939), that the failure to render the blood tests negative was more marked following the use of Trisodarsen and bismuth than after Trisodarsen alone.

This compound appears to have given favourable results but, as the authors remark, the series has not been observed long enough to evaluate definitely the probabilities of "cure" in syphilis.

Phenarsine hydrochloride

This new addition to our antisyphilitic weapons is a mechanical mixture of one part by weight of 3 amino 4 hydroxyphenyldichlorarsine hydrochloride and 3·5 parts of dry sodium citrate as a buffer. It is readily soluble in water with which it forms a clear solution. The arsenical compound contains 25·8 per cent of arsenic although the final mixture contains about six per cent. Although phenarsine hydrochloride in the dry form does not contain arsenoxide, this compound is formed on the addition of distilled water, when the hydrochloric acid and alcohol in the molecule are split off. The fact that phenarsine hydrochloride in the dry form contains no arsenoxide is of importance from the standpoint of stability.

This compound which was reported upon as regards its toxicity in animals by Ewins and Everett in this *Journal* in 1927 has recently been the subject of several clinical reports.

Tompsett, Downs, McDermott and Webster (1941) have treated 126 cases of early syphilis with this remedy. They report that the compound is a safe and effective agent in the treatment of syphilis. Early syphilitic lesions heal rapidly and *S. pallida* disappear speedily.

In recent months there have been three reports (Kampmeier and Henning, 1943 ; Long, 1943 ; Guy, Goldmann and Gannon, 1943) of the action of this compound under the name of Clorarsen or of phenarsine hydrochloride. In general the three reports agree that phenarsine hydrochloride is both a safe and an effective arsenical in weekly, or in some instances twice weekly doses of 0·045 to 0·067 grammes, over a period of six to twelve weeks.

The rate of healing of early syphilitic cutaneous lesions appears to vary in the reports from two to five weeks, probably on account of the well-known difficulties in deciding when a syphilitic lesion has healed. It is evident that rapid healing

took place in some of the cases. All three reports are in agreement that serious toxic effects do not occur. Regular blood picture studies in the series reported by Guy, Goldmann and Gannon failed to reveal any untoward effects. Nausea was a frequent complaint although vomiting appeared rare.

The effect of this compound on the positive serology is judged by various tests including Wassermann (Kolmer technique), Kahn and Hinton reactions. Kampmeier and Henning found eighty-six per cent of their primary cases were serologically negative at about the twelfth week of treatment. In the secondary stage cases this reversal was noted in seventy-five per cent at the end of the same period. All three reports deal with short period observation and sum up in a general agreement that this compound is of considerable value in syphilis but that long period observation is desirable.

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STRICTURE FORMATION TWO YEARS AFTER SULPHONAMIDE TREATMENT OF GONORRHOEA

M10845, male, aged 27, reported on the 20th April, 1943. The only history of previous venereal disease admitted was that two years ago he had suffered from an uncomplicated gonorrhoea, of four days' duration, following exposure fourteen days previously. He had received oral sulphonamides (four grammes daily for nine days) without concomitant local treatment. The discharge ceased in a day or two, and did not recur; he remained under observation subsequently for about six weeks.

During the past four months he had noticed progressive difficulty in commencing micturition, diminution in the size of the stream and increasing frequency. For the past four weeks urgency of micturition, terminal dribbling and a deep pain in the perineum had occurred.

On examination there was a slight mucoid urethral discharge, the urine was clear, the first portion only containing a few mucoid threads. The prostate was normal. Urethral and prostatic smears showed a small number of pus cells. No gonococci were detected. The blood Wassermann reaction and gonococcal complement fixation test were negative.

Urethroscopy revealed a bridle stricture on the floor of the bulbous urethra approximately half an inch distal to the triangular ligament. The stricture admitted a size 4 F. gum-elastic bougie with difficulty. Dilatation was uneventful. The perineal pain and the other symptoms were immediately relieved.

The interest of this case lies in the fact that a submucous infiltration leading to stricture formation may occur despite the apparently successful chemotherapy of an early gonorrhoea. It also emphasizes the necessity for the inclusion of a competent urethroscopy in the tests of cure.

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